

## Remarks

### I. Status of the Application and Claims

At the time that the present Office Action was mailed, the claims pending in the application were claims 28-47. Claim 34 has been cancelled herein. Thus, the claims now pending are claims 28-33 and 35-47.

### II. The Amendments

Claim 28 has been amended to require that the hydrogenation reaction be performed in the presence of a solvent consisting of a mixture of water and an alcohol. With regard to support for this amendment, the Examiner's attention is directed to claim 34 which has now been cancelled. Claim 39 was amended to maintain consistency. Claim 44 was amended so that it also is limited to a hydrogenation reaction performed in a solvent consisting of a mixture of water and an alcohol. Entry of all of these amendments is respectfully requested.

### III. Claim Objections

On page 7 of the Office Action, claims 29-31 are objected to based upon their being dependent on a rejected base claim. In response, Applicants have amended claim 28 in a way that they believe makes the claim nonobvious.

## The Rejections

On pages 2-7 of the Office Action, the Examiner maintains a rejection of claims 28 and 32-47 claims under 35 USC § 103 as being unpatentable over Minnaard, *et al.* (*Synthetic Communications* 29:4327-4332 (1999)) in view of Schuda, *et al.* (*J. Org. Chem.* 53:873-875 (1988)). The reasons why the Examiner did not find Applicants' arguments with respect to these references to be persuasive are set forth on pages 2 and 3 of the Office Action as follows:

Applicant's arguments, filed September 10, 2010, with respect to the rejection of claims 28 and 32-47 under 35 USC 103 as being unpatentable over Minnaard, *et al.* in view of Schuda, *et al.* have been fully considered and are not found to be persuasive. Applicants have requested that the Examiner provide an explanation of why the pending 103 rejection was introduced, withdrawn and then reintroduced. The reason is because the Examiner withdrew the rejection previously in error. Applicants provided mere arguments on August 14, 2009 arguing the differences between the instant invention and the prior arts' teachings. For example, using a rhodium catalyst, Minnaard reports a 92% yield after a

reaction of 40 hours and using a platinum catalyst, Schuda reports a reaction that proceeds for 18 hours and that appears to produce a yield of 98%. Whereas the same types of products under similar conditions, Applicants report yields of 94.2%-98.6% after reaction times that are less than half of those reported in the references. The Examiner wants to point out that merely modifying the process conditions which includes concentration, temperature, reaction times, etc. is not a patentable modification absent a showing of criticality (See *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955)). Further, Applicants have not provided comparative data in the originally filed specification or in a declaration showing unexpected results. Mere arguments are not enough to show unexpected or unobvious results. According to MPEP 716.01 (b), attorney's arguments cannot take the place of evidence on the record. And if Applicants want to show unobvious or unexpected results, they are suggested to show the unobvious or unexpected results in the form a declaration. The reasons above are why the Examiner has reintroduced the pending 103 rejection and why Applicants' arguments filed on September 10, 2010 do not overcome the rejection. The Examiner has maintained the rejection in this Office Action claims 28 and 32-47. The Examiner has withdrawn the 103 rejection of claims 29-31 because claims 29-31 are drawn to subset of compounds that are not taught in the prior art references.

#### **A. Response with Respect to Claims 28-40 and 44-47**

The hydrogenation reaction as set forth in amended claims 28-40 and 44-47 is performed in a solvent consisting of water and an alcohol. This may be compared with Schuda which, in the "Experimental Section" under the subsection "2-Amino-3-hexahydro-phenylpropionic Acid (3)," states:

A solution of 50.00 g (0.303 mol) of L-phenylalanine (2) in 200 mL of glacial acetic acid and 140 mL of water was treated with 2.50 g of platinum oxide and the mixture of [sic] hydrogenated at 45 psig of hydrogen at 50°C for 18 h on a Parr shaker apparatus.

This reaction, performed in a concentrated solution of acetic acid, differs significantly from that claimed by Applicants in claims 28-40 and 44-47 both with respect to catalyst and solvent.<sup>1</sup>

The solvent required in Applicants' claims 28-40 and 44-47 also differs from that disclosed in the reaction of Minnaard (see page 4329 in Minnaard, lines 11-13). In endnote 10, Minnaard states "In our hands, hydrogenation of (S)-2 with Pt/C in aqueous HCl afforded

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<sup>1</sup> Schuda indicates that, at one point, methanol and additional acetic acid were added. However, this appears to have been done to dissolve a semisolid mass formed after the reaction mixture had been cooled to room temperature. Thus, Applicants believe that the addition was after the hydrogenation reaction was complete.

a greenish solution and large amounts of catalyst were needed for the reaction to reach completion.” This suggests that the reaction referred to was found to be inefficient (“large amounts of catalyst were needed for the reaction to reach completion”) and may have resulted in the formation of undesired side products (“afforded a greenish solution”). The inclusion of the solvent system in the statement of endnote 10 suggests that Minnaard views it as an important element with respect to the results obtained.

Overall, a person of skill in the art, would have to make at least two choices in order to arrive at the invention of claims 28-40 and 44-47. Starting from a prior art publication disclosing a first catalytic metal (either Minnaard or Schuda), such a person would have to both choose to include the second catalytic metal and, in addition, choose a different solvent system. Both of these choices relate to features from the field of chemistry and, in Applicants’ experience, this is usually regarded by the PTO as an unpredictable field. Thus, Applicants respectfully request that the Examiner reconsider these claims in light of the present amendments and, in particular, consider whether it would be obvious for one of skill in the art to make these particular choices and whether, prior to experimentation, the resulting combination would have a reasonable prospect of resulting in a successful reaction.

#### **B. Additional Comments with Respect to Claims 28-47**

The Examiner suggests that Applicants’ have merely offered arguments for patentability. However, these arguments are based on a comparison of the results reported by Applicants for reactions which utilize a platinum-rhodium mixed catalyst with results reported by the cited references for reactions performed using different catalysts.

Specifically, in Example 1 of the application, Applicants report on the production of D-cyclohexylglycine. It was found that, after approximately 6 to 8 hours, hydrogen uptake was complete (see paragraph [0055])<sup>2</sup> and that the reaction produced a yield of 95.8-97.7% (see paragraph ([0057])). Example 2 is concerned with the production of L-cyclohexylalanine. In this case, the application reports that, after approximately 6 to 8 hours, hydrogen uptake is complete (see paragraph ([0059 ])) and that there was a yield of 94.2% (see paragraph ([0060])). In Example 3, a reaction was carried out in which (2R, 1'RS)-3-(3'-piperidine) alanine X 2HCl (2R,1'RS)-2-amino-(3'-piperidine) propionic acid X 2HCl) is produced. Here

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<sup>2</sup> The paragraph numbers are taken from the published application, *i.e.*, US 2006/0205954.

hydrogen uptake was completed after about 4 hours (see paragraph [0061]) and there was a yield of 98.6% (see paragraph [0062]). Example 4 describes a reaction in which L-cyclohexylglycinol X HCl is produced. After approximately 6-8 hours, hydrogen uptake was complete (see paragraph [0063]) and the yield was found to be 96.1% (see paragraph [0064]).

The results above may be compared to those reported in the references recited by the Examiner for reactions which employed different catalysts. Minnaard reports on the synthesis of enantiomerically pure cyclohexylglycine using rhodium on carbon (Rh/C) as the catalyst (see page 4329, lines 11-13 from the top). The reference reports a yield of 92% after 40 hours of reaction (see page 4329, lines 15-16 and page 4330, lines 9-11). The Schuda reference appears to describe the hydrogenation of phenylalanine in the second paragraph under the "Experimental Section" on page 874. Using a platinum oxide catalyst, Schuda reports a yield of 98% after about 18 hours (see subsection entitled 2-Amino-3-hexahydrophenylpropionic Acid (3)).

Thus, Applicants are not relying on Attorney arguments alone in responding to the Examiner's rejections. By comparing the results in the references cited with the results in the application, it should be apparent that Applicants report yields comparable to those of the cited references in less than half of the time reported by Schuda and in less than one fourth the time reported by Minnaard. This is a substantial difference and, since Applicants are not using the same catalysts as those in the cited references, is not simply the result of optimizing the reaction conditions of Schuda or Minnaard.

It should also be noted that Applicants' claims expressly require a process that produces a yield of greater than 94% after a reaction time of about 6 to 8 hours. There is nothing in the cited references that suggests that the reaction procedures described in those references are capable of this.

Overall, Applicants respectfully submit that the Examiner has not established prima facie obviousness for the claims under consideration.

### Conclusion

In light of the considerations above, Applicants respectfully submit that all of the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,

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